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EDITORIAL COMMENT

Connectivity of Radiotracers to Vasodilators

Is Thallium the Missing Link?*

Vasken Dilsizian, MD

Baltimore, Maryland

In clinical practice, when new radiotracers receive U.S. Food and Drug Administration approval, there is a tendency to presume that comparable sensitivity and specificity for the detection of coronary artery disease (CAD) between radiotracers, for example, thallium and sestamibi, extends to other clinically and prognostically relevant parameters, such as comparable size and severity of perfusion defects on stress (summed stress score) and extent

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of reversibility when compared with rest images (summed difference score). Although 2 radiotracers may show a perfusion defect in a particular coronary artery vascular territory with stress, the size and severity of the defect and the extent of defect reversibility may be significantly different depending on the extraction fraction of the radiotracer and the point of the plateau phase at higher blood flow rates. Such data are generally not captured when using only sensitivity and specificity and coronary angiography as the reference standard for detecting CAD.

Clinical and Prognostic Relevance of Myocardial Perfusion Defect Size and Reversibility

The extent and severity of reversible myocardial perfusion defects has been repeatedly shown to be an independent variable in predicting subsequent cardiac events in the literature. Among patients with suspected CAD and no prior myocardial infarction who were followed up for 1 year after myocardial perfusion imaging, stepwise logistic regression identified only 3 independent predictors of subsequent cardiac events: 1) the number of regions with reversible defects (extent of myocardial ischemia); 2) the magnitude of hypoperfusion (severity of the perfusion defect); and 3) the achieved heart rate (reflecting the exercise workload) (1). The cardiac event rate increased in a curvilinear fashion as a function of extent and severity of reversible defects.

It has been well established that all 3 clinically approved and available single-photon emission computed tomography (SPECT) radiotracers (thallium, Tc-99m–labeled sestamibi and tetrofosmin) can differentiate patients showing normal perfusion at peak stress with <1% annual rate of death or infarction from those with abnormal myocardial perfusion scans with event rates that are in proportion to the extent and severity of ischemia and scar. Whether the extent and severity of perfusion defects among subjects with abnormal scans is variable among the 3 radiotracers has not been well studied in the literature. The latter distinction becomes clinically pertinent, however, if coronary artery revascularization is being contemplated for purposes of improving prognosis. The extent and severity of myocardial ischemia can guide whether the patient's risk is high enough to warrant revascularization. Such a risk-based approach for medical or revascularization therapy requires accurate determination of the true extent of underlying myocardial perfusion defect and its reversibility.

Efficacy Studies of Vasodilators With SPECT Radiotracers

In the case of the recently approved adenosine receptor subtype A_{2A}-selective agonist, regadenoson, among 2,015 patients from 2 identical double-blind, randomized, multicenter phase 3 ADVANCE

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From the University of Maryland School of Medicine, Baltimore, Maryland.

(ADenoscan Versus regAdenosoN Comparative Evaluation for Myocardial Perfusion Imaging) trials, regadenoson administered as a fixed-unit bolus was shown to be noninferior to adenosine infusion for the detection of reversible defects (2). Given that the aim of the ADVANCE trial was to test the efficacy of the vasodilators and not the radiotracers, it was appropriate for subjects to receive the same radiotracer(s) in the adenosine–adenosine and adenosine–regadenoson comparison to limit other confounding variables, such as differences in the biodistribution and extraction fraction of the radiotracers. Because all 3 clinically available SPECT radiotracers were used in the trials, it has been generally assumed that there are no differences among these 3 radiotracers when used with regadenoson for detection of coronary artery disease or for assessment of the extent and severity of relative perfusion defects. The latter, however, was not tested in the clinical trial.

In this issue of *iJACC*, Mekkaoui et al. (3) compare the vasodilatory effects of regadenoson with adenosine in clinically relevant instrumented canine models, using thallium and sestamibi as the radiotracers. Similar to adenosine infusion, the investigators found that bolus injection of regadenoson produced comparable hemodynamics effects and similar biodistribution and clearance kinetics of thallium and sestamibi. The arterial blood clearance half times with regadenoson and adenosine were significantly faster for sestamibi (mean 1.4 to 1.5 min) than for thallium (mean 2.5 to 2.7 min), which may have implications on the duration of vasodilator stressors when using thallium as the radiotracer. However, despite the differences in blood clearance, thallium performed better as a perfusion agent than sestamibi for the detection of relative flow heterogeneity with regadenoson, as defined by ex vivo SPECT and well counting techniques. Although both radiotracers underestimated the true myocardial blood flow heterogeneity when compared with microspheres, part of the underestimation of thallium could be attributed to the 15-min time delay between injection of thallium and assessment of myocardial uptake, allowing for the well-recognized phenomenon of thallium redistribution to take place. In contrast, the underestimation of sestamibi likely reflects its lower extraction fraction when compared with thallium rather than tracer redistribution (Fig. 1).

On the basis of these experimental findings, the investigators suggest that thallium may offer a clinical advantage over the Tc-99m–labeled perfu-

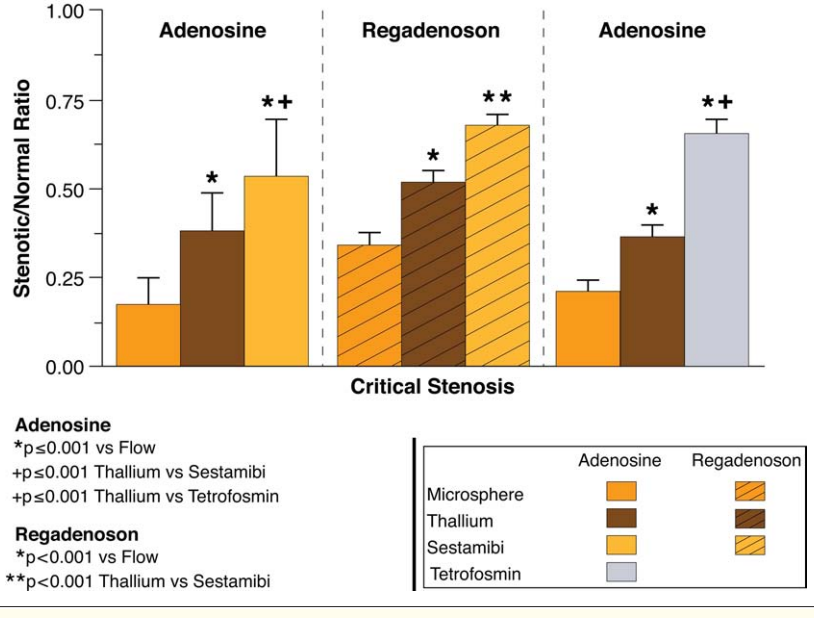

Figure 1. Underestimation of Myocardial Blood Flow by SPECT Radiotracers When Compared With Microspheres

Bar graphs showing mean microsphere flow, thallium, and sestamibi activities expressed as the stenotic-to-normal thallium and sestamibi ratios for critical coronary artery stenosis with adenosine **(left)** and regadenoson **(middle)**. Although both thallium and sestamibi significantly underestimate blood flow when compared with microsphere flow, the degree of underestimation is significantly greater for sestamibi when compared with thallium (3,6). Similar results are obtained using a different technetium-99m–labeled perfusion tracer, tetrofosmin, in comparison with thallium and microsphere with adenosine **(right)** (7). Adapted and reprinted, with permission, from Mekkaoui et al. (3), Glover et al. (6), and Glover et al. (7). SPECT = single-photon emission computed tomography.

sion tracers. The more linear myocardial uptake of thallium during regadenoson vasodilation than sestamibi may have clinical implications regarding the extent and severity of myocardial perfusion defects and for predicting future cardiac events. If these differences in myocardial flow heterogeneity and defect size with thallium and sestamibi are reproduced with regadenoson in the clinical setting, it would be important to revisit using thallium protocols in clinical practice, especially among patients who weigh <220 lbs.

Experimental and Clinical Evidence for Underestimation of Flow Disparity With Tc-99m–Labeled Radiotracers

An ideal radiotracer must have high first-pass extraction by the heart (>50%) and rapid clearance from the blood (clearance half time of <5 min). The radiotracer that most closely parallels myocardial blood flow would be expected to most accurately identify CAD. The extraction fraction of thallium is approximately 85%, whereas that of sestamibi is near 60%. Because the extraction of sestamibi is less than that of thallium at resting flow rates, further decreases in extraction at higher flows (>2 $ml \cdot min^{-1} \cdot g^{-1}$), as with pharmacologic vasodilatation, may lead to an underestimation of the size and magnitude of perfusion defects when compared with thallium (4).

Using vasodilator stimulation in canines, Leon et al. (5) compared the extent of myocardial perfusion defect size with thallium and sestamibi using post-mortem staining to define the extent of the hypoperfused region. When coronary artery occlusion was near total, sestamibi and thallium showed similar defect contrast and areas. However, when coronary artery occlusion was moderate, counts in the defects were 39% higher for sestamibi compared with the thallium defects, and the area of the sestamibi defects occupied only 37% of the area of the defect on the thallium images. The extent of hypoperfused myocardium determined pathologically was closer to the thallium than the sestamibi defect size (5).

Similar underestimation of the true myocardial blood flow deficit was reported in canine models with critical and mild coronary artery stenosis, euthanized 5 min after the injection of thallium and sestamibi (6). Although myocardial uptake of both thallium and sestamibi seemed to plateau at high coronary flow rates, the extent of underestimation of coronary blood flow was statistically greater with sestamibi (leveling off approximately 2× normal flow), resulting in limited contrast between normal and stenotic myocardium (Fig. 1). When the coronary artery stenosis was severe, the ratios of stenotic to normal activity by well counting for thallium (0.37 ± 0.05) and sestamibi (0.53 ± 0.06) underestimated the microsphere-determined flow disparity (0.17 ± 0.03) ($p < 0.005$), but the degree of underestimation was greater for sestamibi ($p = 0.001$). Similar results were obtained using a different technetium-99m–labeled perfusion tracer, tetrofosmin, in comparison with thallium and microsphere (7) (Fig. 1). Such underestimation of flow disparity with sestamibi and tetrofosmin persisted (in comparison with thallium and microspheres), even when milder degrees of coronary artery stenosis were applied (6,7).

In large clinical studies, the sensitivity and specificity of thallium and sestamibi were shown to be comparable for the detection of CAD. However, beyond detection of CAD, whether the myocardial perfusion defect size, severity, and reversibility are also similar between thallium and sestamibi remains controversial. When sestamibi and thallium were injected in the same subjects during stress, sestamibi myocardial perfusion defects were consistently smaller than thallium regardless of whether the sestamibi images were acquired 120 min (8) or 60 min post-stress (9). Patients undergoing symptom-limited exercise stress testing showed smaller sestamibi defect sizes than with stress thallium imaging (42 ± 39.9 g vs. 52 ± 46.2 g, $p < 0.05$) (8). Similar underestimation of defect size was obtained by other investigators when tetrofosmin was used (instead of sestamibi) as the comparator with thallium (10).

Conclusions

Selection of the ideal radiotracer with a pharmacologic vasodilator requires in-depth understanding of the physical and physiological properties of the radiotracer, the vasodilator, the interconnectivity between the two, and the SPECT camera. With the advent of high-speed SPECT cameras, lower doses of thallium (2.0 to 2.5 mCi) can now provide excellent image quality with a radiation burden that is similar to that of technetium-99m–based myocardial perfusion protocols (11,12). Thus, the weakest link for the connectivity of radiotracers with vasodilators may rest in the extraction fraction of the radiotracer and the point of the plateau phase at higher blood flow

rates. Whether thallium will perform better than sestamibi in the clinical setting, as a perfusion agent, for the detection of relative flow heterogeneity with regadenoson and for defect reversibility is a laudable goal to pursue.

Reprint requests and correspondence: Dr. Vasken Dilsizian, University of Maryland Medical Center, 22 South Greene Street, Gudelsky Building, Room N2W78, Baltimore, Maryland 21201-1595. *E-mail: vdilsizian@umm.edu.*

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